REMARKS

Claims 14, 15, 19 and 21-27 are active in the present application. Support for Claims 21-27 is found in Claims 14, 15, and 19 and the specification on pages 26-27. No new matter is believed to be added by these amendments.

Applicants wish to thank Examiner Wilson for the courteous telephonic discussion granted to Applicants' undersigned U.S. representative on September 19, 2001.

During this discussion the Examiner requested clarification as to the construction of the ΔV3 mutants, to which the undersigned pointed to the specification on page 26. The details of the construction protocol is provided below. In addition, to address the Examiner's concern that the specification only describes a V3 mutant in a HIV-1 IIIB strain, the undersigned noted that the specification, and particularly the Examples, illustrate the importance of deleting the V3 region for inducing cellular immunity against viral infection and thus one of skill in the art can extend these teachings to other HIV isolates. The Examiner indicated he would reconsider the enablement rejection.

The Examiner also requested clarification as to the difference between the WTP clones and ΔV3 clone, to which the undersigned noted that in Applicants' previous response it was explained that WTP refer to wild-type clones and Δ3 refer to V3 deletion clones (referring to page 5 of Applicants Request for Reconsideration filed on April 11, 2001).

Lastly, with respect to the enablement of the vaccine as claimed in this application, the Examiner indicated that providing either a showing that *in vitro* CTL responses correlate to *in vivo* CTL response or other evidence demonstrating that the Δ3 mutants provide *in vivo* protection against viral infection, he would reconsider the rejection. Therefore, Applicants have provided a manuscript submitted for publication that demonstrates *in vivo* protection with the Δ3 mutants, which will be discussed in more detail below.

In view of the discussion summarized above, the claim amendments submitted herein and the following remarks, favorable reconsideration and allowance of the pending claims is requested.

The rejection of Claims 14, 15, 19 and 20 under 25 U.S.C. § 112, first paragraph ("written description") is traversed.

The first issue the Examiner alleges that the specification lacks a description concerning the construction of the V3 mutants. This allegation is **not** correct.

Applicants direct the Examiner's attention to the specification on pages 26-27, which clearly describes the construction of the deletion constructs. The details are summarized below:

- "The vv-Δ3 mutant with the Δ297-329 deletion was constructed by ligation of fragments obtained by PCR amplification from the pSCIII-env plasmid." (Page 26, lines 16-18).
- The PCR primers utilized for this construction are shown on page 26, line 19 to page 27, line 7.
- The specification further teaches that the fragments were ligated into a pSC11 vector on page 27, lines 7-9).
- The plasmids pSC-ΔV3 were used vv-ΔV3 constructs by homologous recombination referring to Earl et al on page 27, lines 12-14).

Therefore, one of skill in the art, following this detailed procedure can make the V3 deletion mutants and in so doing that a peptide sequence was provided in the deleted V3 region to maintain the three-dimensional structure of the envelope glycoprotein. Applicants further note that this is the same procedure described by the inventors in the *Journal of Immunology* 1998 Jun 1;160(11):5676-83, a copy of which is appended herewith.

The Examiner also alleges that the specification does not disclose how to make the 1ΔV3, 7ΔV3 and 8ΔV3 mutants nor how they are different (page 4 of the Official Action). Likewise, the Examiner alleges that the specification does not disclose how the WTP clones are different from the 1ΔV3, 7ΔV3 and 8ΔV3 mutants. These allegations are **not** correct.

The specification clearly discloses that the 1ΔV3, 7ΔV3 and 8ΔV3 mutants are different recombinant clones (designated by number) obtained following the homologous recombination procedure described in the specification on page 27, lines 12-14, also see page 34, lines 19-21: "a set of recombinant vaccinia viruses was constructed with complete and V3 loop deleted env genes" and page 35, lines 1-5. Therefore, the 1ΔV3 mutant is the first clone obtained after homologous recombination, the 7ΔV3 is the seventh clone obtained after homologous recombination, etcetera.

The "WTP" clones are wild-type clones, that is those that do not have a deletion in the V3 region. The construction of the WTP clones is described on page 27, lines 9-12. It is known in the art that WT refers to wildtype or non-mutant clones as evidenced, for example, in the attached Journal of Immunology article attached herewith. Therefore, the WT clones are different from the Δ3 clones by virtue of not having a V3 deletion mutation.

The Examiner has also alleged that the specification does not disclose using the vectors to induce cellular immune response in a patient or that a "cellular immune response is directed toward HIV or that such effect is therapeutic or prophylatic" (page 4 of the Official Action). These allegations are **not** correct.

On page 3, line 20 to page 5, line 9, the specification discloses that the invention is to induce cellular immunity in patient having a modified immunodominant epitope and vaccines as well. The immunodominant epitope is described on page 3, lines 3-5. In addition, the

specification on page 41, line 21 through page 42, line 7 describes the vaccination with the ΔV3 mutants, "which will also reduce the need for immunization with HIV strain-specific env glycoproteins." These ΔV3 mutants may be delivered as plasmid DNA (page 42, line 1) or cells expressing the mutated env product (ΔV3, page 42, lines 4-6). Likewise, the specification discloses "The fact that the ΔV3 mutant interacted with anti-gp-120 antibodies of HIV-infected individuals suggests that it is capable of inducing antibody responses *in vivo*" (page 42, lines 5-7).

Lastly, the Examiner contends that "the specification does not teach how to modify the envelope glycoprotein of any strain of HIV other than HIV-IIIB" (page 4 of the Official Action). Applicants disagree and direct the Examiner's attention to MPEP § 2163.02:

> An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

The present invention is based on the discovery that the deletion of the V3 region of the HIV envelope glycoprotein results in increased CTL responses, which are directly correlatable to protection against HIV infection. Sequences of HIV isolates are known in the art and the specification provides a detailed explanation of constructing V3 deletion mutants. Therefore, in light of the disclosure provided in the specification one of skill in the art recognizes that the invention is based on the discovery of deleting the env V3 region in HIV, inclusive of, but not limited to HIV-IIIB.

In view of the foregoing, Applicants submit that the present claims are adequately described within the meaning of 35 U.S.C. § 112, first paragraph. Therefore, withdrawal of this ground of rejection is requested.

The rejection of Claims 14, 15, 19 and 20 under 35 U.S.C. § 112, first paragraph ("enablement") is traversed.

The Examiner has alleged two main points; (1) the mutants are not adequately described; and (2) the *in vitro* CTL responses shown in the specification do not correlate to *in vivo* protection against viral infection (see pages 5-11 of the Official Action). The details of the V3 mutant construction are summarized above. Therefore, the remaining issue is whether the correlation between *in vitro* CTL and *in vivo* protection can be made in light of the documents cited by the Examiner (Ross, Verma, Haynes, Stricker and others). Applicants attach to this response, a manuscript (Kiszka et al), which has been submitted for publication, demonstrating (A) induction of CD8+ T cell activities and (B) increased resistance to viral transmission in transgenic mice, i.e., *in vivo*. These findings are summarized in the Abstract found on page 2 of the manuscript. The data presented in this manuscript demonstrate that the *in vitro* observations described in the present application do, in fact, correlate to both *in vivo* CTL responses and *in vivo* protection via immunization with the V3 deletion mutants.

Therefore, Applicants submit that the skilled artisan can make and/or use the claimed invention without undue experimentation and as such the claimed invention is enabled within the meaning of 35 U.S.C. § 112, first paragraph.

In view of the foregoing, withdrawal of this ground of rejection is requested.

The objection to the specification under 35 U.S.C. 132 is obviated by amendment.

Applicants submit that the present application is now in a condition for allowance. Early notification of such is earnestly solicited.

Respectfully submitted,

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IN THE SPECIFICATION

Page 26, replace the text beginning at line 12 with the following paragraph:

--The HIV-1IIIB isolate was the source of the full-length env gene and the ΔV3 loop mutant cloned in the pSCII-based vector under the control of a synthetic early/late vv promoter (Earl et al, 1990, Removal of cryptic poxvirus transcription termination signals from the human immunodeficiency virus type 1 envelope gene enhances expression and immunogenicity of a recombinant vaccinia virus. *J Virol. 64:2448-2451*). The vv-ΔV3 mutant with the Δ297-329 deletion (15 [Wyatt, R.M. et al, *J. Virol. 66:6997-7004*], incorporated by reference herein in its entirety) was constructed by ligation of fragments obtained by PCR amplification from the pSVII-env plasmid (a gift from Dr. J. Sodroski, Dana-Farber Cancer Institute, Boston, MA). One fragment was generated by PCR with the synthetic oligonucleotide containing the *Sal*I site and the CCACC Kozak's sequence in front of the ATG codon (5'-AGAGTCGACCCACCATGAGAGTGAAGGAGA-3', sense) (SEQ ID NO:1), and the oligonucleotide (5'-ACAGGTACCCCATAATAGACTGTGAC-3' antisense) (SEQ ID NO:2) containing the *Kpn*I side, used for ligation with the second env fragment. The second fragment was derived by *Kpn*I and *Bam*HI digests fo the pSVIII-env plasmid, and the third fragment was generated by PCR with the synthetic oligonucleotide containing the *Bam*HI site at its 5' end (5'-AACGGATCCTTAGCACTTATCTGGG-3',

sense) (SEQ ID NO:3) and the antisense primer (5'-TTGCGCGGCCGCTTATAGCAAAATCCTTTCC-3') (SEQ ID NO:4) containing the TAA stop codon followed by the *Not*I site. The three fragments were ligated into the *Sal*I and *Not*I sites of the pSC11-based vector (a generous gift of Dr. L. Eisenlohr, Thomas Jefferson University, Philadelphia, PA) to generate plasmid pSC-ΔV3. A similar approach was used to generate plasmid with the WT env gene (pSC-WTP) using recombinant clone pIIIB (Hwang, et all, *Science* 253:71-74) kindly provided by Dr. B. Cullen (Howard Hughes Medical Institute, Duke University Medical Center, Durham, NC). Plasmids pSC-ΔV3 and pSC-WTP were used to generate vv-ΔV3 and vv-WTP by homologous recombination as described (Earl et al, 1990, *J Virol. 64:2448-2451*).--

IN THE CLAIMS

Claim 20 is canceled.

Claims 21-27 are added.